

Remarks

In response to the Office Action mailed on December 10, 2009, the Applicant presents herewith facts and explanations showing that the claims on file have adequate written description complying with the 35 U.S.C. § 112, 1st paragraph, that no new matter has been introduced into the claims and that the claims 58-59 and 64-67 rejected as being anticipated by Dudek et al (USP No. 6,291,516) are not anticipated by it or by other prior art.

I. Claim Rejections – 35 U.S.C. § 112 - 1st Paragraph

1. Claims 44-57, 60-63, 68-69

Claims 44-57, 60-63 and 68-69 have been rejected stating that specification does not have adequate description of the claimed methods of treating a tumor wherein Hedgehog/Smoothed (Hh/Smo) signaling is utilized for inhibition of apoptosis of tumor cells by administration of cyclopamine or of another selective inhibitor of Hh/Smo signaling in a dose sufficient to induce apoptosis of the tumor cells and to cause decrease of size or disappearance of the tumor. Examiner stated that requiring the skilled artisan to carry out random, hit-or-miss testing of varying doses of cyclopamine or of another selective inhibitor of Hh/Smo signaling to determine what doses are sufficient to induce tumor cell apoptosis and decrease of size or disappearance of a particular tumor is evidence of lack of compliance with the written description requirement. It was concluded that the specification does not therefore provide adequate written description of the claimed doses, other than those of cyclopamine as disclosed in the working examples with basal cell carcinoma tumors. The rejection is traversed.

In determining compliance with the written description requirement "the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art, as of the filing date sought, applicant was in possession of the invention as now claimed" (MPEP 2163). Analysis of compliance includes "a determination of ... the level of skill and knowledge in the art"; "information which is well known in the art need not be described in detail in the

specification" (*Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ81, 90 (Fed. Cir. 1986), cert denied, 480 U.S. 947(1987)). "There is nothing inherently wrong with defining some part of an invention in functional terms. Functional language does not, in and of itself, render a claim improper" (*In re Swineheart*, 439 F.2d 210, 169 USPQ226 (CCPA 1971)). "Possession ... may be shown in a variety of ways including description of an actual reduction to practice ... or by describing distinguishing identifying characteristics" (MPEP 2163; see e.g. *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000)).

Examiner's statement that the specification lacks written description support concerning optimization of the dose of a non-cyclopamine compound to carry out the invention amounts to stating that Applicant did not have written description of a subject matter that is routinely practiced and common knowledge in the art and also turns a blind eye to the actual disclosure in the specification. The following are excerpts from a medical textbook published more than 20 years before the filing of application (*Review of Medical Pharmacology*, 7th edition Meyers FH et al, Lange Medical Publications, Los Altos, CA, U.S.A., 1980). "[R]esponse of any given patient to a drug will be subject to individual variation ... With most drugs ... each drug administration becomes an exercise in bioassay to establish the dose that will have a therapeutic effect without intolerable or dangerous toxic effects" (page 22, right column, last paragraph). A person of ordinary skill in the art routinely administers a drug to a patient in a dose expected to produce a known effect, starting at a level lower than that required in order to achieve the desired therapeutic effect and gradually increasing until the desired effect is achieved. The skilled person is well versed in optimization of doses of prior art drugs for a particular patient once he or she knows what effects are to be produced and knows, as the specification of application mentions, that "optimal dosing and application schedules ... can be determined by following well known published optimisation methods" (page 11, lines 10-15). Take the example of treatment of diabetes mellitus. In treatment of this common disease, administration of one of several structurally unrelated compounds that exert the lowering of blood glucose as a common, unifying functional feature has long been practiced. Dose of a particular anti-diabetic drug for a patient is adjusted by monitoring the effect on blood glucose. Even patients, once taught, can self-monitor

their blood glucose and can self-administer a suitable dose of a drug (see e.g. Birkeland KI, *Diabetic Medicine* 1998;15:S13-S19).

In treatment of tumors, state of the art at the time of application was such that effect of prior art treatments on a tumor could be reliably monitored. Monitoring size of a tumor by imaging modalities, obtaining biopsies for various analyses and determining tumor markers in blood and other body fluids were common knowledge and routinely practiced in prior art. Assays to determine differentiation and/or apoptosis of tumor cells were also common knowledge. Therefore, a skilled person informed about causation of a particular desired effect on a tumor by administration of a drug could readily optimize the dose of drug for a patient to obtain the described effect. See for example Cannavo S et al, *Journal of Endocrinological Investigation* 1999;22:354-359 describing use of a new drug for treatment of patients having pituitary tumor. Prolactinomas are pituitary tumors known to produce symptoms both due to the growing tumor mass and due to the secreted hormone. Various dopamine agonists varying in structure were used in prior art for treating patients bearing prolactinoma. Cannavo et al (*ibid*) decided to use a new dopamine agonist, cabergoline, for treatment considering its favorable pharmacokinetics. They started treatment of patients at a dose of 0.5 mg/week and monitored its effect on serum prolactin, a tumor marker for these tumors. In 8 of 37 patients said dose was effective to bring down serum prolactin to normal along with the shrinking or disappearance of the tumor that was monitored by magnetic resonance imaging (MRI). In those patients not showing normalization of prolactin, dose was increased step-wise at 0.5 mg/week steps until the lowest dose effective to achieve normalization of serum prolactin was reached. Cannavo et al (*ibid*) describe that serum prolactin could be normalized in 8/37 patients with 0.5 mg, in 15/37 with 1.0 mg, in 5/37 with 1.5 mg, in 3/37 with 2.0 mg, in 2/37 with 3.0 mg and in 1/37 with 3.5 mg per week dose of drug and the tumor monitored by MRI was shrunken or disappeared.

Level of skill and knowledge in the art at the time of application was such that a skilled person could readily optimize the dose of a compound even when having a narrow therapeutic window above which it is lethal. Soignet SL et al (*New England Journal of Medicine* 1998;339:1341-1348) describe use of arsenic trioxide for treatment of acute promyelocytic leukemia (APL)

patients by monitoring the effect of administered dose on neoplastic cells in serially obtained bone marrow biopsies and in blood as well as on the normal cells and physiological functions of patients. They started with a minimal dose and gradually increased it until identifying the lowest dose that was effective to produce the previously reported effect of the elimination of APL cells from blood and bone marrow of patients. Median daily dose that was found to be effective to eliminate neoplastic cells from bone marrow was 0.16 mg/kg in 11 patients and ranged from 0.06 mg/kg to 0.20 mg/kg in individual patients (more than 3 fold difference from one patient to the other). Dosing was continued for 24 to 83 days in individual patients for reaching to the desired therapeutic result (disappearance of detectable neoplastic cells from patient) and the cumulative amount of arsenic trioxide administered to reach to said result varied from 160 mg to 515 mg (Soignet et al, *ibid*). Thus, the level of skill in the prior art was such that even a compound showing marked variation from one patient to the other in its effective dose and that is well known to become lethal when increased only about one third from the described 0.20 mg/kg/day dose could be administered to patients to achieve an expected therapeutic effect without causing intolerable adverse effects.

It is clear that structurally varying compounds having a unifying functional feature were widely used in prior art for treatment of a given disease, including tumoral, and adjusting dose of a member of a functionally defined class of compounds for achieving a known and expected effect in a patient was routine. Not only a skilled person but even a patient could adjust the dose of a drug to obtain a particular effect after being taught about it. A specification is addressed to persons skilled in the art and does not need to detail what is well known or routine in the art.

Teachings In The Specification Satisfying The Written Description Requirement

Specification has written description that the claimed effects and therapeutic results are dosage dependent and that non-cyclopamine compounds exerting the described biological and therapeutic effects of cyclopamine are also suitable to use for treatment.

See page 19, lines 2-4 summarizing results of actual treatments of human patients: "*Thus,*

while the tumor response to optimal concentrations of cyclopamine was rapid, suboptimal concentrations could not induce ... apoptosis ... of tumor cells".

See likewise page 15, line 27 to page 16, line 12 describing that, in the same tumor, the tumor region and tumor cells exposed to relatively lower concentrations of cyclopamine were relatively unaltered and did not show detectable apoptosis of tumor cells while the tumor region to which cyclopamine cream was applied directly to supply a greater dose regressed rapidly in association with induction of apoptosis of the tumor cells.

Another most telling description in the specification for a skilled person is the description that normal tissue cells, including those known to be the normal stem cells and progenitor cells that are particularly damaged by the prior art chemo-radiotherapy of cancer, were perfectly spared by a dose inducing differentiation and massive apoptosis of the tumor cells. See e.g. page 6, lines 21-28; page 9, line 26 to page 10, line 4; page 15, lines 4-17; Fig. 4A to 4D. Specification refers to said feature and teaches that "*Preservation of the undifferentiated cells in the normal epidermis and hair follicles ... provide information about the tolerable doses in other possible modes of administration ... e.g. ... systemic administration*" (page 11, lines 22-27). In prior art, a skilled person knew that systemic administration of drugs is used for internal tumors. In addition he or she sees a direct teaching that "*Causation of highly efficient ... apoptosis of the tumor cells in vivo ... at doses that preserve the undifferentiated tissue cells ... support the use ... on those internal tumors that utilize the hedgehog/smoothened pathway ... for preservation of apoptosis*" (page 15, lines 19-24). Notice the presence of written description that is explicit concerning treatment of internal tumors. Notice also that the internal tumors to be treated are those "*that utilize the hedgehog/smoothened pathway ... for prevention of apoptosis*" (page 15, lines 19-24).

When presented with said teaching, it becomes fully clear to a skilled person what is it that he or she is to do to induce apoptosis of the tumor cells. A skilled person clearly understands from said teaching that a selective inhibitor of Hh/Smo signaling is to be used to achieve apoptotic elimination of the tumor cells and to obtain decrease of size or disappearance of such tumors in patients. See also page 19, lines 24-29 teaching that "*functional preservation as well of the*

(normal) *stem cells and long-term safety ... facilitates treatment of internal tumors*". Hence, a skilled person finds direct teaching in the specification that the described treatment is suitable for treatment of non-BCC tumors by administration of a sufficient dose of cyclopamine or of another selective inhibitor of Hh/Smo signaling to induce apoptosis of the tumor cells to obtain decrease of size or disappearance of the tumor.

Contrary to the mistaken opinion of Examiner that the specification does not have written description of treatment with a sufficient dose to provide decrease of size or disappearance of non-BCC tumors, the specification does have it. See page 17, lines 4-9 describing "*Another noteworthy finding in this patient was the decreased size ... of a mole located nearby ... on the 24th hour of treatment ... the mole (a ... melanocytic tumor) appears to be sensitive to relatively low concentrations of cyclopamine*". The treatment is described to cause disappearance of melanocytic nevi in another subject as well (page 17, lines 9-11).

Specification of the application teaches directly and unambiguously that a non-cyclopamine compound exerting the biological/therapeutic effects of cyclopamine described in the specification is suitable to carry out the invention. See page 10, lines 8-10 stating "*molecules can be ... synthesized in such a way that they ... exert ... biological/therapeutic effects of cyclopamine*". A skilled person understands clearly that the non-cyclopamine compounds taught to be suitable to carry out the invention are functionally defined. Specification makes clear that the structural features given on page 10, lines 9-22 for a compound derivable from cyclopamine are not exclusive ("*may include*") and that exertion of the cyclopamine effects described in the specification is a pre-condition ("*provided that*").

Cyclopamine used to exemplify the invention was known in prior art to be a teratogenic Veratrum alkaloid that inhibits Hedgehog/Smoothed (Hh/Smo) signaling directly and selectively. See page 3, first paragraph of the specification mentioning said well known biological effect of cyclopamine and referring to relevant prior art publications and see also the incorporated priority document PCT/TR02/00017, page 3, lines 1-7 for further prior art. The referred Incardona JP et al, *Development* 1998;125:3553-3562 and Cooper MK et al, *Science*

1998;280:1603-1607 publications had described that cyclopamine as well as other teratogenic Veratrum alkaloids inhibit Hh/Smo signaling directly and selectively (Incardona et al, *ibid*, page 3553, Summary; page 3557, left column, last paragraph; page 3560, left column, 1st paragraph; Cooper et al, *ibid*, page 1603, Abstract; page 1606, left column, paragraphs 1-2). In prior art the Smoothed protein (Smo) was known to be absolutely necessary for the signaling initiated by a Hedgehog (Hh) protein in a target cell (hence the name Hh/Smo signaling in this application) and evidence was obtained that cyclopamine inhibits Hh/Smo signaling at the level of Smo (see page 1006 of the Taipale J et al, *Nature* 2000;406:1005-1009 publication referred on page 3, first paragraph of specification). Cyclopamine treatment was recognized to cause the same phenotype in developing embryos as by a targeted genetic elimination of Shh (see e.g. Incardona et al, *ibid*, page 3560, 1st paragraph "*Cyclopamine treatment thus produces a phenocopy of a Shh loss-of-function mutation*"). Selective targeted genetic elimination of a signaling protein in an animal is an ultimate selective or specific inhibition of the involved signaling. Furthermore, precisely the same Shh-induced molecular events inhibited by cyclopamine and by a genetic loss of Shh expression were shown in prior art to be selectively inhibited also by function-blocking monoclonal and affinity purified anti-Shh antibodies (Ericson J et al, *Cell* 1996;87:661-673; see page 662, left column, paragraphs 2 and 3 for proof of selectivity of inhibition; Incardona et al, *ibid*, also describe use of the same antibodies to bind Shh). Hence, it was common knowledge in prior art that cyclopamine or a structurally related or unrelated compound can be used to inhibit Hh/Smo signaling selectively and the scientific publications referred in the specification under "Background Of The Invention" have their descriptions.

Prior art had also description of adjustment of doses of selective inhibitors of Hh/Smo signaling to obtain a previously known effect on cells. See for example Taipale et al (*ibid*) referred in the specification of application describing dose-response curves showing adjustment of the dose of cyclopamine and of another selective inhibitor of Hh/Smo signaling to achieve maximal inhibition of proliferation of the neoplastic cells having constitutively activated Hh/Smo signaling (page 1007, Figure 3).

It is clear from the foregoing that state of the art at the time of application was such that a

person of ordinary skill in the art could readily adjust the dose of a drug for a patient once informed about the effect to be produced with it. Specification of application has ample written description showing that the presently claimed effects and therapeutic results are dose-dependent (see also Appendix A of 03.18.2009 Amendment) and has unambiguous written description that a non-cyclopamine compound exerting the biological/therapeutic effects of cyclopamine described in the specification is suitable to carry out the invention. *"Use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds ... a functional recitation of those known compounds in the specification may be sufficient as that description"* (*In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 285 (CCPA 1973)).

Adjusting doses of prior art medicaments for a patient to achieve a previously known effect is a routine for a skilled person. Further, specification has clear description and exemplifications of a target effect, namely induction of apoptosis of the tumor cells to achieve decrease of size or disappearance of a tumor that utilizes Hh/Smo signaling for inhibition of apoptosis of tumor cells. From that starting point, adjusting the dose appropriate for a patient is not "hit-or-miss" but a routine in the art.

Withdrawal of the rejection of claims 44-57, 60-63, 68-69 is requested in view of the foregoing facts and explanations showing that the specification of application has adequate written description satisfying 35 U.S.C. § 112, paragraph 1.

2. Claims 58-59, 64-67

Claims 58-59 and 64-67 have been rejected as failing to comply with the written description requirement, stating that the "instructions for effective administration" recitation in the claims are found nowhere in the originally filed disclosure. The rejections are traversed.

Instructions are implicit or inherent for prescription drugs. Provision of instructions for health care professionals with prescription drug product packages is legally mandated in most states

throughout world. In the U.S.A., for example, the Food, Drug and Cosmetic Act of 1938 (21 U.S.C. § 301 et seq. 52 Stat. 1040) forming the nucleus of today's law relating to pharmaceutical products required labeling containing adequate directions for use of such products. Amendments to the 1938 FDCA have kept that requirement. The US Food and Drug Administration provided with authority to implement regulations for that purpose states that the package insert (also called professional labeling or prescription drug product insert) "must accompany the drug product and contains the essential scientific and medical information needed for safe and effective use of the drug by health care professionals". See e.g. 21 C.F.R. §§ 201.56, 201.57 and 201.100.

Specification of present application certainly has extensive instructions concerning how to carry out the described treatment (see I.1 above). Pharmaceutical products for use in the treatment are also described (see e.g. page 4, lines 12-17; page 10, line 8 to page 11, line 27; originally filed claims 13-22). To satisfy the written description requirement "*there is no haec verba requirement, newly added claim limitations must be supported in the specification through express, implicit or inherent disclosure*"; "*To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described*" (MPEP 2163; *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-1951 (Fed. Cir. 1999)).

Considering that instructions for use had long been an integral part of prescription drugs in prior art and that persons of ordinary skill in the art would recognize that a prescription drug product insert having such instructions is necessarily provided with such drugs, claims 58-59 and 64-67 do comply with the written description requirement and do not introduce new matter. Withdrawal of the rejections to claims 58-59 and 64-67 under 35 U.S.C. § 112, paragraph 1 is requested.

II. Claim Rejections – 35 U.S.C. § 102(e)

Claims 58-59 and 64-67 have been rejected under 35 U.S.C. § 102 (e) as being anticipated by Dudek et al (USP No. 6,291,516; Dudek et al'516). Examiner referred to *In re Ngai*, 367 F.3d 1336, 13339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004) and *In re Gulack*, 703 F.2d 1381, 1385-86, 217 USPQ 401, 404 (Fed. Cir. 1983) to state that since the instructions in the present

medicament claims are not functionally related to the claimed product, claims 58-59 and 64-67 are anticipated by Dudek et al'516. The rejections are traversed. Dudek et al'516 does not anticipate any of said claims and does not anticipate for multiple reasons.

(i) In the *Gulack* case, the Court decided allowance of a product claim where a new and unobvious functional relationship was found between the printed matter and substrate of it. In the *Ngai* case, *Ngai* had described a new method of amplifying and normalizing RNA and claimed a kit for normalizing and amplifying an RNA population, comprising previously known compounds and instructions describing *Ngai*'s method. The Court, like the *Gulack* Court, looked to see whether there exists any new and unobvious functional relationship between the printed matter and the substrate. Finding none, the Court affirmed rejection of *Ngai*'s claim to the kit.

Both cases that have been referred by the Examiner support patentability of present claims 58-59, 64-67. As noted in item I.2 above, instructions are implicit or inherent for prescription drugs and are legally mandated in the U.S.A. and most other states throughout world. Notice that in case of *Ngai*, amplified-normalized RNA populations were prepared in prior art by methods other than *Ngai*'s new method. *Ngai* developed a new method to obtain amplified-normalized RNA; the end result (amplified-normalized RNA) is the same as in prior art. In the present situation, however, content of instructions is functionally related to the product and it is also clear that previously unknown and unobvious technical effects and therapeutic results are obtained by following the instructions. Without the instructions of present medicament claims, a skilled person does not obtain described apoptosis of the tumor cells and does not obtain the therapeutic results that follow and that are recited in the claims. In prior art, a skilled person using a medicament described by Dudek et al'516 would obtain an inhibition of Hedgehog signaling in tumor cells and would obtain an inhibition of tumor growth through inhibition of tumor cell proliferation (see the 03.18.2009 amendment for analysis of Dudek et al'516 as a whole; see said and previous amendments also for analysis of the rest of prior art). However, the facts on record show that causation of Hh/Smo signaling does not make differentiation or apoptotic elimination of the same cells anticipated or obvious (see e.g. the 03.18.2009 amendment). It is further clear that the therapeutic results recited in claims 58-59 and 64-67 cannot be achieved by causation of an

inhibition of tumor cell proliferation. In addition, it is self-evident that the recited technical effects and therapeutic results would not be obtained without a medicament recited in the claims. Hence, a functional relationship exists between the printed matter and the substrate and the claims 58-59 and 64-67 are not anticipated by Dudek et al'516 or by other prior art.

(ii) Dudek et al'516 discloses on the one hand an unlimited number of compounds ("subject compounds") that are said to inhibit or upregulate Hedgehog (Hh) signaling and mention on the other hand a virtually unlimited number of disorders that are said to be treated by administration of a subject compound. Except where the nature of a subject compound (an inhibitor or upregulator of Hh signaling ?) is clear or can be deduced by a skilled person, the teaching is ambiguous. Further, even in those situations where the nature of a compound to be used can be understood clearly, the teaching is inoperative in entire categories (see the 03.18.2009 amendment). Hence, a skilled person must carry out undue amount of experimentation just to determine an operative teaching apart from those that are inoperative in Dudek et al'516 and the teaching is lacking enablement. "[S]ignificant numbers of inoperative embodiments would render ... nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative" (*Atlas Powder Co. v. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984)).

(iii) The Smoothed protein (Smo) was known in prior art to be obligatory for the signaling initiated in a target cell by a Hedgehog (Hh) protein and it was unambiguously demonstrated that Hh/Smo signal transduction has a single end point, the Ci/Gli proteins that serve as transcriptional activator or repressor of Hh target genes depending on their phosphorylation-dependent proteolytic processing (Methot N et al, *Development* 2001;128:733-742). The converse was also investigated and it was found that activities of Ci/Gli proteins can be affected by non-Hh/Smo signals as well (Methot et al, *ibid*). The findings that protein kinase A (PKA) and glycogen synthase kinase 3 β (GSK3 β) both negatively regulate the Ci/Gli transcriptional activator function (see e.g. Wang QT et al, *Development* 2000;127:3131-3139 and Motzny CK et al, *Mechanisms Of Development* 1995;52:137-150) and that both of these kinases have multiple substrate proteins had provided an explanation for the effects of non-Hh/Smo signals on Ci/Gli proteins. Thus,

several different mitogenic signals were found to act on GSK3 β to downregulate it and to relieve the GSK3 β substrate proteins from GSK3 β mediated phosphorylation and proteolysis (see e.g. Diehl AJ et al, *Genes & Development* 1998;12:3499-3511). Since the substrates of GSK3 β included cyclin D1 and β -catenin (which is required for Wnt/ β -catenin signaling), it was clear that this kinase could regulate responses to multiple signals promoting cellular proliferation (Diehl et al, *ibid*). Similarly, it was well recognized that whereas phosphorylation of Ci/Gli proteins by PKA promotes their proteolytic processing to inhibit transcription of Hh target genes, upregulated PKA phosphorylates many other proteins as well and PKA certainly lacks a selective action on Hh/Smo signaling (see e.g. Wang et al, *ibid*). For decades, it was common knowledge in prior art that binding of cyclic AMP (cAMP) to PKA activates its kinase (phosphorylating) activity. Further, many hormones were known to affect cellular cAMP content and changes in cellular cAMP content were known to affect numerous cellular functions. Thus, it was clear in prior art that a single obligatory transducer (Smo) and a single end point (Ci/Gli) make Hh/Smo signaling ideally suited to selective inhibition but cAMP or analogs or "agonists" thereof or PKA or GSK3 β are unsuitable. Dudek et al'516 does not describe use of a selective inhibitor of Hh/Smo signaling to obtain a presently described and claimed technical effect or therapeutic result and its claims are directed to uses of a "cAMP agonist".

(iv) Presently claimed invention is not inherently present in prior art. Inhibition of proliferation of various cell types, including tumor cells, by treatment with a selective inhibitor of Hh/Smo signaling was known in prior art. See e.g. Fujita E et al, *Biochemical and Biophysical Research Communications* 1997;238:658-664 referred to in Dudek et al'516 (col. 44, line 64 to col. 45, line 11) describing a dose-dependent inhibition of proliferation of human lung cancer cells by treatment with a selective inhibitor of Hh/Smo signaling. No induction of differentiation or apoptosis of said tumor cells is described even though the proliferation-inhibited tumor cells were examined by microscopy which ordinarily allows detection of said effects when caused. See the 03.18.2009, 02.20.2008, 06.11.2007 and 01.10.2007 dated amendments and the Declaration attached to the latter showing that use of a selective inhibitor of Hh/Smo signaling to achieve inhibition of proliferation of tumor cells does not provide differentiation and/or apoptosis of the tumor cells and that a treatment schedule and dose far beyond that produces inhibition of tumor

cells is required to achieve the presently described and claimed effects and therapeutic results. Declaring the presently claimed invention anticipated by Dudek et al'516 or by other prior art on the basis of an inherent presence of it in prior art is not possible.

(v) In the absence of an inherent presence of a claimed invention in prior art, the factual determination of anticipation requires the disclosure of each and every element of the claimed invention in a prior art document. To be anticipating, a prior art document must in addition enable the claimed invention. Mere naming of a subject matter or of an effect is insufficient for enablement, especially if the cited document's disclosures concerning a claimed subject matter are ambiguous and clearly self-contradictory. Also, just as a skilled person considers a given document as a whole, the law requires consideration of a document as a whole in determination of anticipation. In the absence of an actual result or evidence, *unsupported naming of all potential effects of a treatment, including the precise opposite effects*, in a patent application and *contending that it is enabling regardless of which effect turns out to be true is a deception in disclosure*. This sort of deception is not intended to be allowed by law. Analysis of Dudek et al'516 as a whole shows that in its disclosures made without an evidence or actual treatment result, both inhibition and induction of differentiation of cells and both inhibition and induction of apoptosis of cells are named as effects of a treatment with a Hh antagonist, similar to those in the related Beachy et al USP 7,291,626 and 6,432,970 publications which have largely overlapping disclosures (often identical word-by-word with Dudek et al'516 over extended passages). Said unsupported naming is done even though said publications describe inhibition of differentiation and inhibition of apoptosis effects by Hh antagonists on cells on the basis of the actual treatment results described therein (see the 03.18.2009 and 02.20.2008 amendments for analysis of Dudek et al'516 as a whole and of the related Beachy et al publications as a whole). Further, even when taken at face value, it is clear that an unsupported naming of effects found similarly in Dudek et al'516 (col. 41, line 66 to col. 42, line 4) and in the related Beachy et al publications does not enable and does not anticipate the presently claimed invention (see the 02.20.2008 amendment, page 16).

A skilled person is taught by Dudek et al'516 to use a Dudek et al'516 medicament as

described in it. It is clear however that the skilled person presented with Dudek et al'516 is not enabled to obtain the presently described and claimed technical effects and therapeutic results (see the 03.18.2009 amendment analyzing Dudek et al'516 as a whole and see the same and 02.20.2008 amendment analyzing related Beachy et al publications as a whole).

At least for the aforementioned reasons and for those others articulated previously with the amendments filed in this application, Dudek et al'516 does not anticipate claims 58-59 and 64-67. Withdrawal of the rejection of said claims is requested.

III. Conclusion

The claims have adequate written description complying with the 35 U.S.C. § 112, 1st paragraph and do not introduce new matter. The claims 58-59 and 64-67 are not anticipated by prior art. It is clear that the presently described and claimed invention has brought a highly desirable, novel and unobvious solution to the long-standing problems in prior art in treatment of cancer. Early and favorable action thereon is requested.

Respectfully submitted,
VIDAS, ARRETT & STEINKRAUS

Date: January 21, 2010

By: /Walter J. Steinkraus/
Walter J. Steinkraus
Registration No.: 29592

6640 Shady Oak Dr., Suite 400
Eden Prairie, MN 55344-7834
Telephone: (952) 563-3000
Facsimile: (952) 563-3001